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PHARMACOTHERAPEUTIC EVALUATION OF SACUBITRILWITH VALSARTAN IN HEART FAILURE PATIENTS

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ABSTRACT

Background: In patients with HFrEF, treated with sacubitril/valsartan, the treatment benefits were seen which reflects the LV reverse remodelling and predicts the prognosis. **Objective:** The purpose of this study was to analyse the pharmacotherapeutic evaluation of sacubitril/valsartan in HF patients. **Methodology:** This prospective observational study was performed in the Department of Cardiology, in Aster Prime Hospital, Ameerpet, Hyderabad. The echo parameters such as ejection fraction, mitral regurgitation, diastolic dysfunction, and cardiac enzyme, NT-pro BNP, adverse events, NYHA Classification and quality of life using KCCQ-12 scorewere obtained at baseline and follow-up was done after 3 months. The data recorded were statistically analysed using SPSS version 2020, Chi-square test, dependent-t test and Pearson's correlation. **Results:** Analysis was done in a sample size of 88 patients. Statistical improvement was noticed in ejection fraction, mitral regurgitation and diastolic dysfunction, with a P-valueof (< 0.0001), (0.0080) and (0.0008) respectively, and NT- pro BNP levels was reduced with a P-value of (<0.0001). There is a direct proportional relationship in improvement of KCCQ score with NYHA classification. In this study, it was analysed that 19% of patients improved to NYHA Class 1 after treatment. The impact of sacubitril/ valsartan on KCCQ score domains, the total symptom frequency score, clinical summary score, and overall score show statistical improvement over 3 months, with a P-value of (< 0.0001). **Conclusion:** This study concludes, that after initiation of sacubitril/valsartan, significant changes were observed in echo parameters, and KCCQ-12 score with respect to NYHA class, which minimizes the chances of death and rehospitalization due to cardiovascular complications, with minimal adverse effects thereby indicating improvement in the quality of life and overall health status of the patients.

KEYWORDS: Sacubitril/ valsartan, ejection fraction, NT- pro BNP, Heart failure, NYHA Classification, and KCCQ- 12 score.

1. INTRODUCTION

Heart failure also known as congestive heart failure is a prevalent disease which affects the functions and the ventricle's structure, in turn affecting the quality of life and psychosocial profile of the heart. Myocardial contractility gets augmented by the release of norepinephrine by adrenergic cardiac nerves and the sympathetic nervous system, renin-angiotensin-aldosterone system (RAAS) and other neuro humoral adjustments are activated, that functionsto control arterial pressure and perfusions of essential organs. Myocyte hypertrophy, death/apoptosis, and regeneration is the primary myocardial response to chronically increased wall stress. A cascade of hemodynamic and neuro hormonal derangements that provoke activation of neuro endocrine systems due to the reduction of cardiac output following myocardial injury, RAAS and the other adrenergic systems. This eventually leads to remodelling, eccentric modelling is seen, which further worsens the loading conditions on the remaining myocytes and perpetuates the detrimental cycle. Myocardial energy impairment increases, with a further decrease in cardiac output, due to the increase after load, myocardial contractility and the impairment in myocardial lusitropy.

During heart failure, there is a faster increase in the rate

of myocyte loss such that the mechanism for replacement becomes overwhelmed. The death over regeneration and imbalance of hypertrophy is said to be the most common pathway at the cellular level for the progression of remodelling and heart failure.[1]

Symptoms of heart failure include Congestion of lungs, fluid and water retention, dizziness, fatigue and weakness, palpitations or rapid or irregular heartbeats. They are various aetiologies of heart failure which include, hypertension, coronary artery disease, Heart Attack, Cardiomyopathy, Arrhythmias, Congenital heart defects, Myocarditis, Faulty heart valves, other causes or diseases includes, Obesity, tobacco, illicit drug use. Chronic diseases such as Diabetes, chronic kidney disease, thyroid, valve diseases, some medications that are given as such for chemotherapy, or even hemochromatosis or amyloidosis can also contribute to heart failure.[2]

The most important treatment for heart failure condition can be explained by **New York heart association classification (NYHA):** This is a symptom-based scale that classifies heart failure into four categories. (Table 1)[3]

CLASS	PATIENT SYMPTOMS
I	There is no limitation of physical activity.
II	There is a slight limitation of physical activity. Comfortable at rest.
III	There is a marked limitation of physical activity. Comfortable at rest.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. Physical activity increases discomfort.

Natriuretic peptide system

The natriuretic peptides (NPs) are produced mainly from the cardiomyocytes in response to cardiac stretch during volume or pressure overload. The NPs produced are involved in the maintenance of cardio-renal homeostasis. All the three NPs are metabolised through two main processes, one being NPR-C mediated clearance and the other by an enzymatic breakdown called neprilysin (NEP).

A particular strategy to build-up NP levels and their advantageous effect is by inhibiting NEP, i.e., neprilysin, which metabolizes NPs. Along with NPs, NEP also catalyses the breakdown of angiotensin II, adrenomedullin, substance P, bradykinin, vasoactive intestinal polypeptide. Hindrance of neprilysin would increase circulating levels of NPs, that eventually results in natriuresis, vasodilation, cardiac hypertrophy, diuresis. It also increases levels of angiotensin II, which contributes to sodium retention and cardiac fibrosis stimulation, vasoconstriction. Hence simultaneously, suppression of RAAS is obligatory, Natriuretic peptides help in the regulation of electrolytes, water balance homeostasis and blood pressure levels through diuresis, natriuresis, direct vasodilation, inhibition of RAAS and sympathetic nervous system, increase in glomerular filtration, regulate systemic vascular resistance by inhibiting the vascular smooth muscle contraction, antihypertrophic and antifibrotic myocardial effects. Natriuretic Peptides also plays an essential role by interfering with the analytical mechanisms of atherosclerosis such as angiogenesis, thereby preserving the vascular health in endothelium and vascular smooth muscle cells.[4][5]

Initial neprilysin inhibitors

Oral racecadotril and intravenous candoxatrilat were the initial successful attempts at inhibiting neprilysin, which helped in promoting natriuresis and increasing urinary excretion of ANP.

Candoxatril, an oral prodrug of NEP inhibitor, was clinically a failure as it could not control hypertension and vascular resistances (including pulmonary and systemic) in hypertensive and heart failure patients, respectively. Following which ecadotril (another NEP inhibitor) had similar effects. Ecadotril receiving patients showed more death and side effects.

Neprilysin and ACE inhibition, dual action

Omapatrilat, the first combined ACE and neprilysin inhibitor, initially showed better results when compared to candoxatril in maintaining BP and vascular resistance by the dual blockade of natriuretic peptide system and RAAS. An analytical study of omapatrilat against enalapril 10mg twice daily in a large randomized controlled trial of Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) in which 5770 patients (NYHA class II-IV) were randomized to receive enalapril 10mg twice daily or omapatrilat 40 mg once a day. There was a higher incidence of angioedema reported in the omapatrilat group due to increased levels of bradykinins which led to the cessation of clinical development of omapatrilat.[6][7]

SACUBITRIL/VALSARTAN

PARADIGM-HF, a randomized, double-blind trial, was conducted to examine the effect of sacubitril/valsartan versus enalapril in patients with symptomatic and chronic heart failure. Thetrial showed a relative risk reduction of 20% in the primary end point, a 16% depletion in all-cause mortality, a 21% depletion in risk of hospitalisation for heart failure and a depletion of 23% in total hospitalisation at the closure of the trial. Consequently, sacubitril/valsartan appearto be superior to ACEI enalapril.[6]

Indications

Sacubitril/valsartan has obtained a strong class I (I-BR or IB) recommendation with only one study, i.e., PARADIGM-HF.

It is an FDA approved drug for the treatment of chronic heart failure with reduced ejection fraction (HFrEF, <= 40%) with NYHA class (II-IV) to reduce morbidity and mortality, with systolic bp of >= 100mmHg and eGFR >= 30ml/min/1.73m2 and potassium <= 5.2mmol/l.

Provided that, the patients must tolerate ACEI or ARB before initiating sacubitril/valsartan.[8][9]

Mechanism of action

RAAS is triggered as a maladaptive response in heart failure, which leads to increased sympathetic tone, hypertension, vasoconstriction and increased aldosterone levels leading to cardiac remodelling, all of which are harmful to the progression of the disease. Hence, ACEI or ARBs play an essential role, by reducing the mortality and morbidity due to heart failure, by blocking these maladaptive changes.

The NPS is activated simultaneously as a compensatory mechanism that turns in diuresis, vasodilation, natriuresis and reduces bp, reduces aldosterone levels and lowers the sympathetic nervous system (SNS). This system works antagonistically with the RAAS. Neprilysin, an enzyme, metabolizes natriuretic peptides and are also responsible for the breakdown of angiotensin II, bradykinin, etc. as mentioned earlier.[10][11]

Sacubitril/valsartan (LCZ696) is the first angiotensin receptor neprilysin inhibitor which consists of neprilysin inhibitor prodrug sacubitril (AHU377) and angiotensin II receptor antagonist valsartan. Sacubitrilat (LBQ657), the active metabolite of sacubitril, does not inhibit the aminopeptidase P, and therefore, the risk of angioedema was less expected than the omapatrilat.[6] Valsartan, an ARB works by blocking the RAAS system. Inhibiting neprilysin alone will result in the accumulation of angiotensin II (breakdown inhibition). Hence, it should be used in combination with an ARB to block the effect of increased angiotensin II.

As mentioned above, neprilysin inhibition also results in bradykinin build-up. Hence, sacubitrilshould not be used with that of ACEI, as this increases the possibility of angioedema as a synergistic effect. The patient must undergo a washout period of 36 hrs when changing between ACEI and sacubitril/valsartan (LCZ696) to reduce the risk of angioedema.[12]

Pharmacokinetics

After oral administration, sacubitril has an absolute bioavailability of ≥60% whereas the bioavailability of valsartan is high in combination when compared to regular valsartan tablets. The peak plasma concentration of LBQ657 is 1.9-3.5hrs, for sacubitril is 0.5-1.1hrs and for valsartan is 1.5-2.2hrs.[12]

Sacubitril, valsartan and LBQ657 are highly plasma protein bound with 94%-97%. The volumeof distribution of sacubitril and valsartan is 103L and 75L respectively.

Sacubitril is metabolised to an active metabolite LBQ657 whereas only 20% of valsartan is metabolised.

The mean half- life of sacubitril is 1.1-3.6hrs, 8.9-16.6 hrs for valsartan and 9.9-11.1hrs for LBQ657. The urinary excretion of Sacubitril is 52-68% in urine, 37-48% in faeces. (Primarily as LBQ657) and Valsartan is 13% in urine; 86% in faeces.[13]

KCCQ score

KCCQ is a self-administered questionnaire that the FDA has qualified as a clinical outcome assessment. It is used to independently measure the patient's knowledge about their health status, including symptoms of heart failure, changes or effect on their social and physical function and effect on their QOL within 2 weeks of the recall period.

The KCCQ questionnaire consists of six domains and two summary scores- Symptom domain, Physical function domain, Quality of life domain, Social limitation domain, Self-efficacy domain, Symptom stability domain, Clinical summary score and Overall summary score.

All the scores are represented on a 0-to-100-point scale; the lowest scores represent severe symptoms, and high scores >75 points indicate the excellent quality of life.

To make the KCCQ questionnaire more feasible to implement in our study and to lower the response burden on the patients, we have used a shorter version of KCCQ, KCCQ-12, which is a 12-item tool that preserves the reliability, prognostic interpretability, ability and responsiveness of the original KCCQ 23 instrument.[14][15]

Need of the study

The optimal implementation of this drug in clinical practice can reduce the overall burden of heart failure. Despite the shreds of evidence describing the benefits of ARNI therapy over the standard of care, only a fraction of eligible patients takes sacubitril/valsartan. Several barriers preventing the prescription of sacubitril/valsartan in eligible patients may include physician's unfamiliarity with ARNIs, safety concerns of the patients and overpriced drug combination.

Hence, the patients need counselling for better medication adherence. This study describes ourexperience with sacubitril/valsartan, including the management of adverse effects, reduction of risk factors, lifestyle modification, and prevention of rehospitalization due to worsening of symptoms that may lead to HF.

2. MATERIALS AND METHODS

A Prospective Observational Study was performed to analyse the pharmacotherapeutic evaluation of sacubitril with valsartan in heart failure patients. The study is carried out for a duration of 6 months in the outpatient setting, Department of Cardiology in Aster Prime Hospital, Ameerpet, Hyderabad, Telangana, India. A total of 88 heart failure patients who were prescribed with Sacubitril/Valsartan, were included in our study. The study was conducted with the approval of the Institution Ethical Committee with an Ethics approval no. **AP/EC2021/009.** The study procedure included collection of details in a patient profile form which included, patient's demographics, vitals, diagnosis, patient's prior hospitalization, risk factors, laboratory examinations and 2-Dimensional Echocardiogram (2D ECHO), Possible adverse reactions and drug interactions, Improvement in the quality of life was evaluated using KCCQ-12 tool according to NYHA Classification. Patient counselling for drug adherence and possible beneficial outcomes. The inclusion criteria include, Patients of both gender of age 18 - 75 years, Patients having Hypertension, Diabetes Mellitus as well other comorbidities, Patients with an ejection fraction of less than 45%, Patients who are classified in the NYHA class II, III, and IV. Patients who have undergone Coronary Artery Bypass Graft (CABG), Percutaneous Transluminal Coronary Angiography (PTCA) or Percutaneous Coronary Intervention (PCI). Patient's Sr. Potassium level should be ≤ to 5.1mmol/L and Sr. Creatinine level should be ≤ to 1.2mg/dl. The exclusion criteria, Symptomatic Hypotensive patients, Pregnant and lactating women, postpartum women with heart failure, Patients suffering from viral diseases such as Hepatitis, HIV and severe renal/hepatic impairment.

The prescriptions of 88 patients were collected from the outpatient cardiology department, specified to only heart failure disease, who were prescribed sacubitril and valsartan. The data were collected in the patient profile forms, and the follow up was done after three months, via direct outpatient interview, and telephonic interview, using the KCCQ-12 score, to evaluate the QOL and the patients were counselled for better outcomes. The data collected were compiled using Microsoft Excel 2019 and analysed using version 20 of SPSS software to obtain the graphs and results. The P-value <0.05 is considered significant since the Confidence Interval is 95%. The tests performed were Chi-square test, Dependent t-test, Pearson's Correlation.

3. RESULTS

This observational prospective study was done among 88 patients in a tertiary care hospital inHyderabad.

3.1 Demographics

3.1.1 Gender Distribution

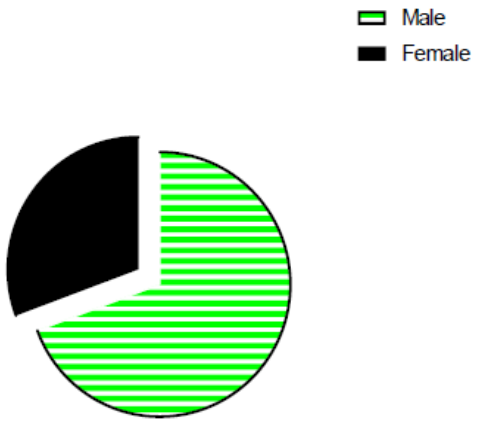

Figure 1.

It has been calculated that out of a total of 88 patients, 69% were male patients (N=61) and 31% were female patients (N=27)

3.1.2 Age Distribution

Table 2.

Age Interval (Years)	Total	Gender		P Value
		Male	Female	
31-40	6(7)	5	1	0.9483
41-50	17(19)	11	6	
51-60	26(30)	18	8	
61-70	26(30)	18	8	
71-80	13(15)	9	4	

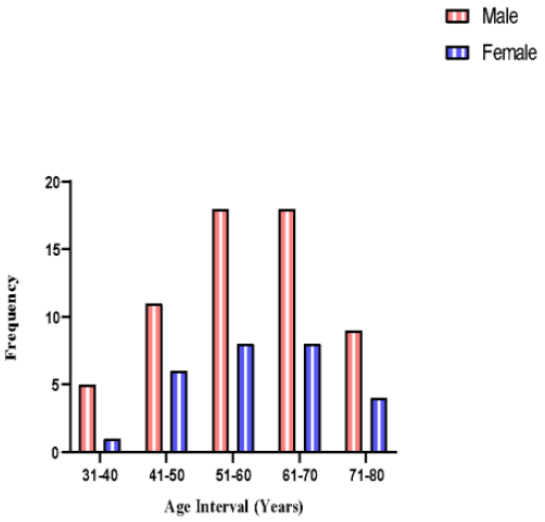

Figure 2.

A statistically significant relationship does not exist. The ages of patients in our study ranged between 31-80 years, out of which 30% (N=26) were between 51-60, 61-70 years of age witha p- value of 0.9483.

3.2 Common diagnosis observed

Table 3.

Diagnosis	Frequency	Percentage
CAD	34	39
ADHF	7	8
AWMI	14	16
DCMP	9	10
RHD	2	2
STEMI	7	8
NSTEMI	4	5
ACS	6	7
CABG	3	3
CHF	2	2

Coronary Artery Disease (39%) is the most common disease diagnosed in our study population followed by Anterior wall myocardial infarction (16%), followed by Dilated cardiomyopathy (10%), followed by Acute decompensated heart failure (8%), followed by ST elevated myocardial infarction with (8%), followed by Acute coronary syndrome (7%), Non ST elevated myocardial infarction (5%), Coronary Artery Bypass Graft (3%) , followed by Congestive Heart failure(2%) and Rheumatic Heart Disease(2%) been the least common diagnosis in the subjects.

3.3 DISTRIBUTION OF COMORBIDITIES AGAINST AGE GROUP OF THEPARTICIPANTS

TABLE 4

Comorbidity	Age Interval					P value
	31-40	41-50	51-60	61-70	71-80	
Diabetes Mellitus	2	7	14	12	8	0.7079
Hypertension	3	11	15	17	10	0.7516
Other	1	1	11	6	6	0.0599

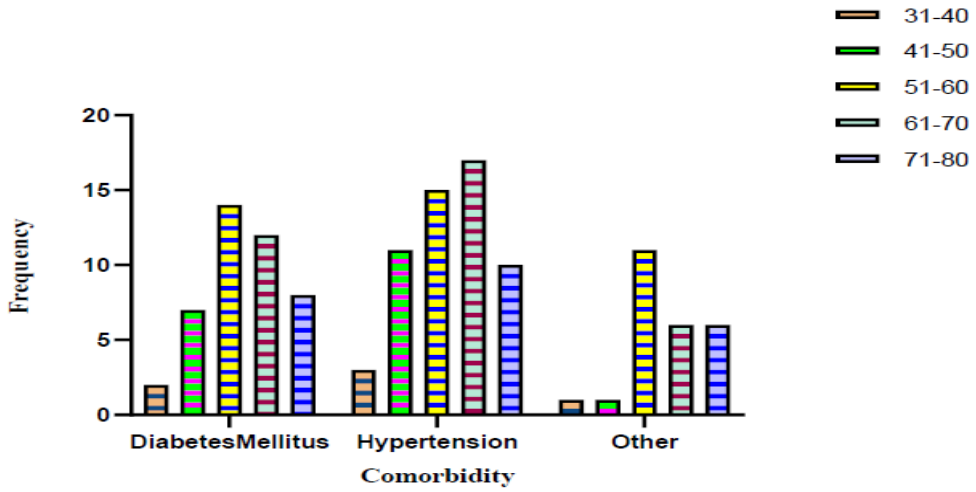

Figure 3.

A statistically significant relationship does not exist between comorbidities and age group ofthe participants.

3.4 Prior hospitalization and re-hospitalization

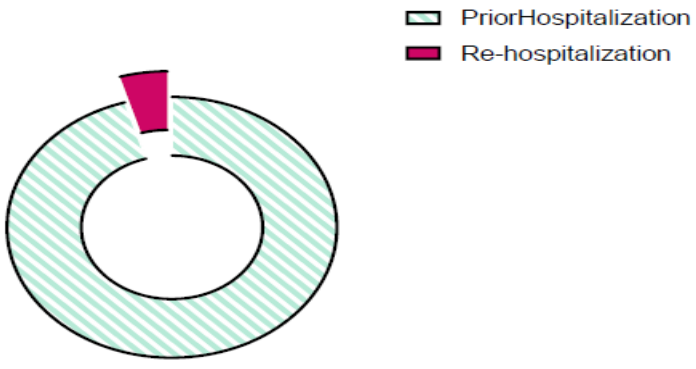

Figure 4.

70% (N=62) patients were hospitalized prior ARNI treatment; 3% (N=3) patients were re-hospitalized post treatment.

3.5 Comparison of NYHA class before and after sacubitril/valsartan treatment

Table 5.

NYHA Class	Treatment		P Value
	Before	After	
1	0(0)	17(20)	<0.0001
2	24(27)	46(52)	
3	55(63)	24(27)	
4	9(10)	1(1)	

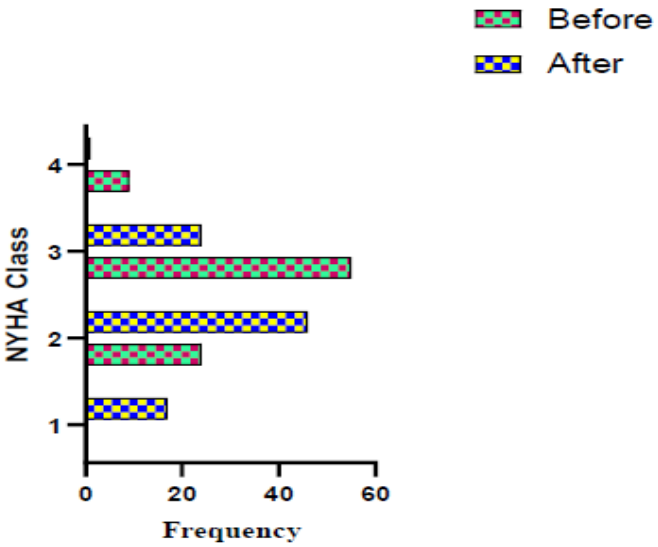

Figure 5.

A statistically significant difference was seen in the NYHA class before and after sacubitril/valsartan treatment with a P- value of <0.0001. For patients in the NYHA Class 1 there was an improvement from 0 to 20% after the treatment, for patients in the NYHA Class 2 there was an improvement from 27% to 52%, where as in NYHA Class 3 & 4 the severity of disease decreased from 63% to 27% and 10% to 1% respectively.

3.6 Comparison of vitals before and after sacubitril/valsartan treatment

Table 6.

Parameter	Treatment		P value
	Before	After	
Blood pressure	136.8 ± 14.57	123.2 ±17.89	<0.0001
Systolic Diastolic	84.69±12.48	76.76±9.74	<0.0001
Heart rate	89.92±12.27	85.81±13.50	0.0006

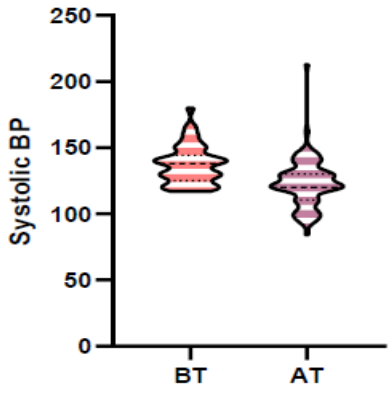

Figure 6

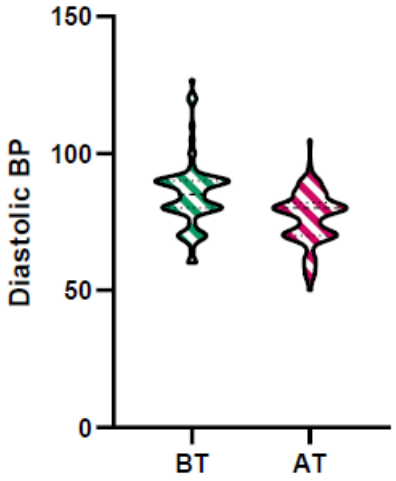

Figure 7.

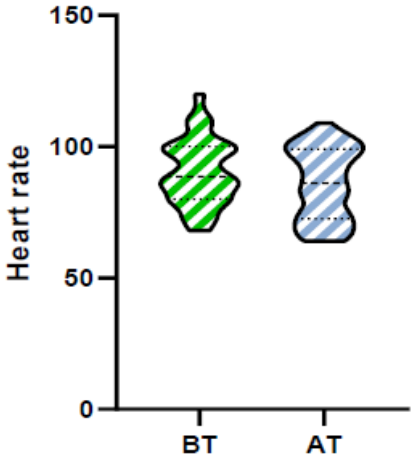

Figure 8.

A statistically significant difference was observed in blood pressure and heart rate after thetreatment with a P-value of (<0.0001) and (0.0006) respectively.

3.7 Comparison of 2D- echo parameters before and after the treatment

Table 7

Parameter	Treatment		P value
	Before	After	
Ejection fraction	34.14±6.00	37.34±6.17	<0.0001
MR			0.0080
Normal	2	5	
Mild	36	55	
Moderate	38	23	
Severe	12	5	
Diastolic			0.0008
dysfunction	17	38	
Grade 1	44	40	
Grade 2	25	10	
Grade 3	2	0	
Grade 4			

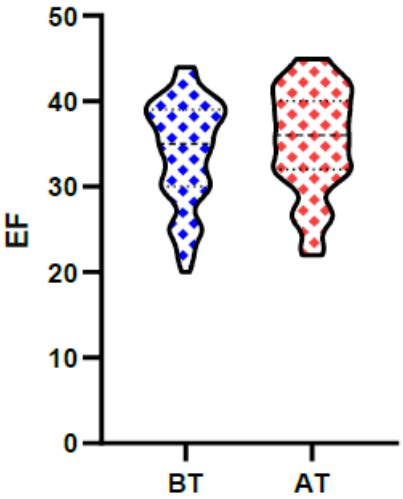

Figure 9

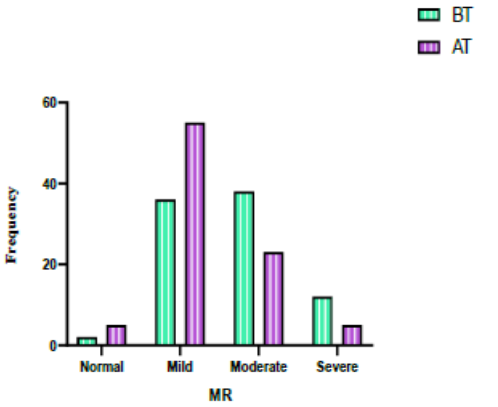

Figure 10.

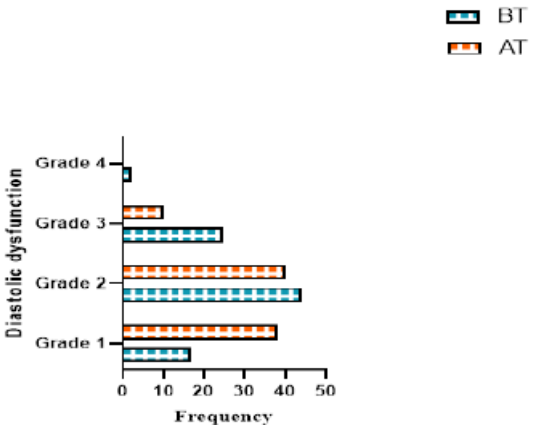

Figure 11.

A statistically significant difference was observed in the 2D echo parameters, which includes ejection fraction with P- value of (<0.0001), mitral regurgitation and diastolic dysfunction with P- value of (0.0080) and (0.0008) respectively.

3.8 Comparison of laboratory parameters before and after sacubitril/ valsartan

Table 8.

Parameter	Treatment		P value
	Before	After	
NT-pro BNP	5573±3488	1357±853	<0.0001
BSR	150.6±85.82	137.2±68.72	0.0003
Serum Potassium	4.24±0.47	3.87±0.41	<0.0001
Serum Creatinine	1.04±0.28	0.91±0.12	0.0016

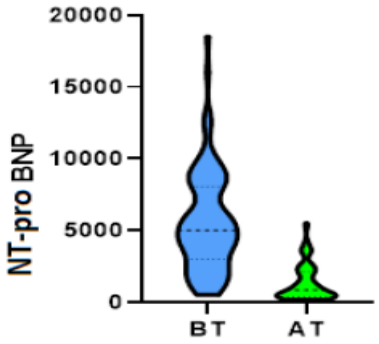

Figure 12

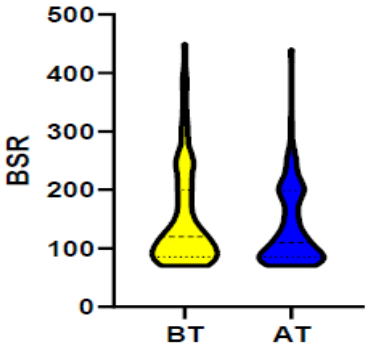

Figure 13

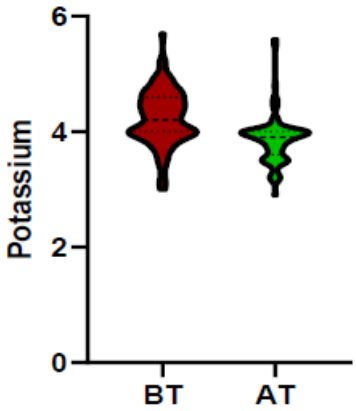

Figure 14

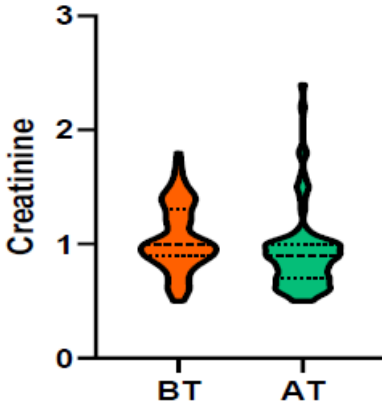

Figure 15

A significant difference was noticed prior and post the initiation of the drug. It has been statistically observed that the NT-pro BNP levels reduced post treatment with a P- value <0.0001. BSR reduced with a P-value of 0.0003, similarly serum potassium and creatinine reduced statistically with a P-value of <0.0001 and 0.0016 respectively.

3.9 Adverse drug reactions

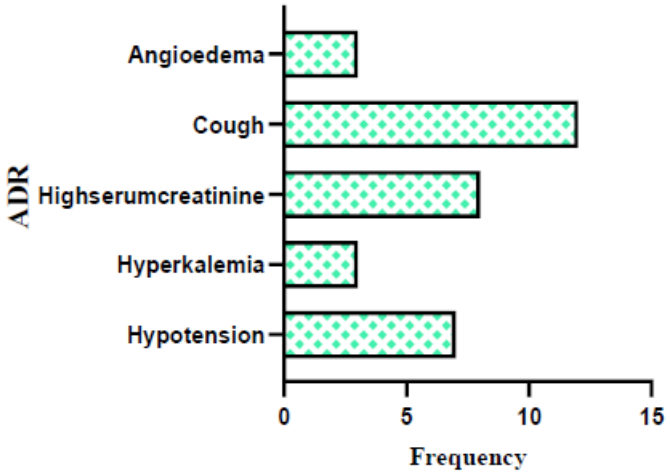

Figure 16.

Adverse drug reactions that were experienced by the patients in our study are – cough (14%), high serum creatinine levels (9%), hypotension (8%), hyperkalemia and angioedema with (3%) respectively.

3.10 KCCQ score based on NYHA class before sacubitril/valsartan treatment

Table 9.

KCCQ Score	Total	NYHA Class			
		1	2	3	4
0-24	8(9)	0	0	0	8
25-49	56(64)	0	0	56	0
50-74	24(27)	0	24	0	0
75-100	0	0	0	0	0

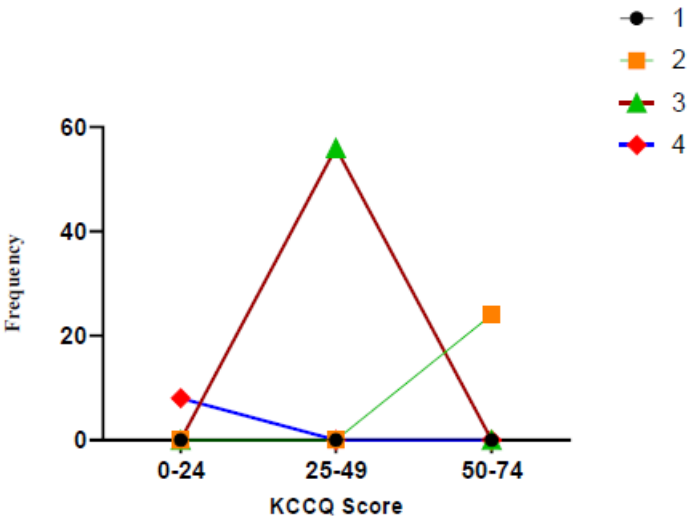

Figure 17.

In the above table it was analysed that 9% of the patients with NYHA Class 4 were classified in 0-24 points, 64% of the patients with NYHA Class 3 were classified in 25-49 points, and 27% of the patients with NYHA Class 2 were classified in 50-74 points. No patients were seenin NYHA Class 1 and were not classified in 75-100 points of KCCQ Score.

3.11KCCQ score based on NYHA class after sacubitril/ valsartan treatment
Table 10.

KCCQ Score	Total	NYHA Class				P value
		1	2	3	4	
0-24	6(7)	0	0	0	6	<0.0001
25-49	17(19)	0	0	16	1	
50-74	48(55)	0	46	2	0	
75-100	17(19)	17	0	0	0	

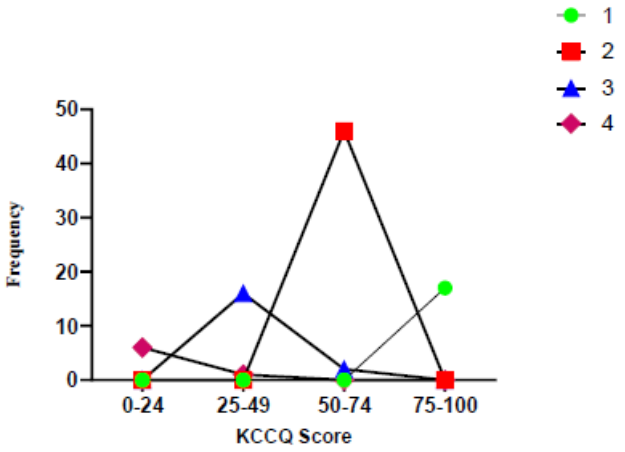

Figure 18.

After the treatment with sacubitril and valsartan patients showed an improvement in NYHAClass, when compared with KCCQ score with a P-value <0.0001.

3.12. Comparison of KCCQ score domains before and after sacubitril/valsartan treatment
Table 11.

Domain	Treatment		P value
	Before	After	
Total Symptom frequency Score	14.51± 4.15	20.67± 4.73	<0.0001
Symptom frequency + Physicallimitation-Clinical Summary Score	24.24± 6.80	33.80± 7.71	<0.0001
Overall Score	39.57± 11.51	56.19±12.50	<0.0001

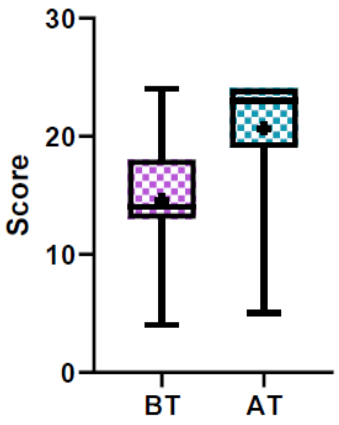

Figure 19: Total symptom frequency score.

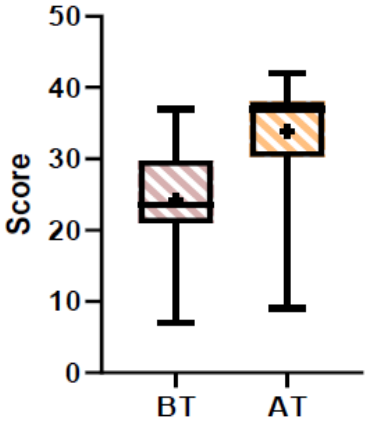

Figure 20: Clinical summary score.

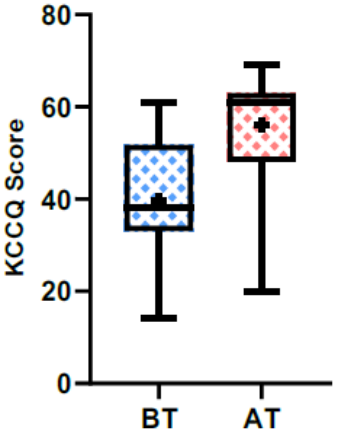

Figure 21: Overall Summary Score.

A statistically significant difference was noticed before and after the treatment in KCCQ Score domains- Total Symptom Frequency Score, Clinical Summary Score and Overall Summary Score With a P- value of < 0.0001 respectively.

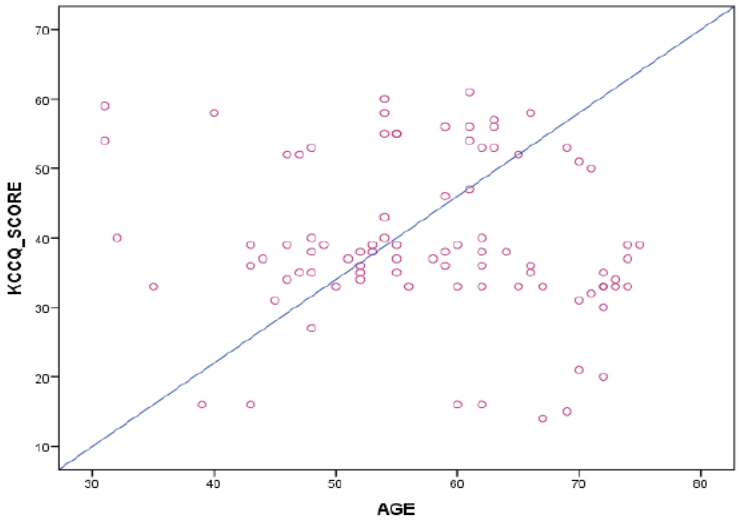

Figure 22: Correlation of Age versus Baseline KCCQ Score.

*y= 1.2 * x + -26*
r= -0.137

For the above graph, Pearson's coefficient was applied, the r- value given is -0.137. A significant inverse relationship was not found between age and KCCQ Score.

4. DISCUSSION

An estimated 17.9 million people died from CVDs in 2019, representing 32% of all global deaths. Around 85% of deaths were due to heart attack and stroke. Over 75% of CVD deaths take place in low and middle-income countries where raised blood pressure happens to be amongst the most important risk factors for CVDs. In 2019 India reported 63% of total deaths due to NCDs, of which 27% were attributed to CVDs. CVDs also account for 45% of deaths in the 40–69-year age group.[16]

This prospective observational study was conducted with a sample size of 88 patients to determine the pharmacotherapeutic efficacy of sacubitril/ valsartan in heart failure patients.

In our study it was analysed that only 3% of the patients were re-hospitalised after the treatment with sacubitril/ valsartan which indicates reduced morbidity and mortality, reduces the risk of death and re-hospitalisation with heart failure. [Figure 4] These results were consistent with the studies done by McMurray, M.D, et al. 2014; 371 and Srikanth Yandrapalli, et al, 2017.[17][18]

In this study the 2D- Echo parameters such as ejection fraction improved from 34.14 ± 6.00 to 37.34 ± 6.17 with a P-value of (<0.0001), mitral regurgitation and diastolic dysfunction, a significant improvement was observed with a P- value of (0.0080) and (0.0008) respectively. [Table 7] [Figure 9, 10, 11] In a study conducted by Peiter martens, et al. 2018, the results showed improvement in LVEF (29.6 ±% vs 34.8±6%) and decrease in LVESV and LVEDV after following up of 118 days after initiation of sacubitril/valsartan. A study done by, Duk- Hyun kang, et al, 2019; 139. The researchers concluded that among patients with secondary functional MR, sacubitril/valsartan reduced MR to a greater extent than valsartan.[19][20]

It was noted that there was a significant difference in NT- pro BNP levels reduced from 5573 ± 3488 to 1357 ± 853, with a P-value of <0.0001. BSR reduced from 150.6 ± 85.82 to 137.2 ± 68.72 with a P-value of 0.0003, serum potassium and creatinine reduced statistically from 4.24 ± 0.47 to 3.87 ± 0.41, with a P-value of <0.0001 and from 1.04 ± 0.28 to 0.91 ± 0.12, with a P-value of P-value of 0.0016 respectively. [Table 8] [Figure 12, 13.14,15] The study conducted by James L. et al, 2019 had similar results which were associated with reduction in NT- pro BNP following initiation of sacubitril/ valsartan. In another study conducted by Akshay S. Desai, MD, MPH, et. Al, 2019 also showed improvement in cardiac biomarkers such as NT- pro BNP.[21][22]

After initiation of the drug the patients had minimal and non-serious adverse drug reactions, that were cough (14%), high serum creatinine levels (9%), hypotension (8%), hyperkalemia and angioedema with (3%) respectively. [Figure 16] The researchers McMurray, M.D, et al 2014; 371, also concluded similar adverse drug effects.

The main objective of our study was to evaluate the quality of life of the patient using KCCQ- 12 Score

Questionnaire, when compared with NYHA Classification. 9% patients of Class 4 reduced to 7% with the lowest scores which indicates poor QOL. 64% patients of Class 3 reduced to 19%, and significant improvement of 27% patients of Class 2 improved to 55% and around 19% of patients improved to Class 1 with high scores of >75 points which indicates excellent quality of life. [Table 9] [Figure 17] [Table 10] [Figure 18] This was in accordance with the studies done by Nael Hawwa, MD et.al 2017[23] and Akshay S. Desai, MD, MPH, et.Al, 2019.

In total symptom frequency score domain patients improved from 14.51 ± 4.15 to 20.67 ±4.73, similarly in clinical summary score domain, patients improved from 24.24 ± 6.80 to 33.80 ± 7.7, and a significant improvement was seen in overall score domain with 39.57 ± 11.51to 56.19 ± 12.50, with a P-value of < 0.0001 respectively. [Table 11] [Figure 19, 20, 21]These results coincided with the studies conducted by Nael Hawwa, MD et.al,2017, Yevgeniy Khariton, et.al, 2019 and Ileana L. Pina MD, MPH, et al, 2020.[24][25]

The patients were counselled, during every follow up, in the outpatient setting department regarding the benefits, functions, advantages, and to enhance medication adherence of the patient.

5. CONCLUSION

This prospective observational study was done to evaluate the pharmaco-therapeutic effect of sacubitril with valsartan in heart failure patients. Our study concludes that the NT-pro BNP levels are significantly reduced in the earlier phase of ARNI treatment, and similarly an improvement was observed in 2D-Echo parameters such as ejection fraction, mitral regurgitation and diastolic dysfunction, within the duration of 3 months. Adverse events such as hypotension, hyperkalaemia, high Sr. creatinine, angioedema, and cough were not significantly higher or severe in patients receiving sacubitril/valsartan. NYHA Classification is used to assess symptom severity in HF patients. After post treatment of sacubitril/ valsartan, a significant improvement was seen in NYHA Class. KCCQ score is a self- administered questionnaire, and it's an FDA approved clinical outcome assessment of functional capacity, and predicts better clinical to outcomes, and hence this tool can be used routinely clinical care, and clinical trials to compute the quality of life, symptoms to evaluate heart failure and social limitation of patients. KCCQ -12 score showed a significant improvement in total symptom frequency score, clinical summary score and overall score. In conclusion sacubitril/valsartan (LCZ696) treatment, appears to be safe and effective in reversing cardiac remodelling with minimal adverse effects and in reducing rehospitalization of heart failure patients to a greater extent and thereby reduction of HF mortality and morbidity, and death due to cardiovascular disease.

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